A Study Towards the Total Synthesis of TAN1251B  
(Kajian bagi Mensintesis TAN1251B Secara Menyuluruh)  

ASNUZILAWATI ASARI* & CHRISTOPHER J. HAYES

ABSTRACT
A synthetic route towards the synthesis of TAN1251B was developed utilizing an alkylidene carbene insertion reaction as a key step to construct the quartenary centre. The α-hydroxylation of the 5,6-spirocyclic enone with iodosobenzene was successful to give a mixture of diastereomer compounds 20 and 21 in 1:1.2 ratios.

Keywords: TAN1251B; alkylidene carbene; α-hydroxylation; iodosobenzene

INTRODUCTION
TAN1251(A-D) (Figure 1) were isolated from a culture of Penicillium thomii RA-89 (Shira Fuji et al. 1992). The structures of these series of compounds contain a unique tricyclic skeleton that consists of a 1,4-diazabicyclo[3.2.1]octane ring and a spiro-fused cyclohexanone ring.

(+)-TAN1251 B (2) is muscarinic antagonist of value as mydriatic or antispasmodic/antiulcer agent that exhibit cholinergic activity and cause acetylcholine-induced contraction of Guinea pig ileum with ED_50 values of 8.0 and 10.0 nM, respectively. The affinity of (+)-TAN1251B for the muscarinic acetylcholine receptor is stronger than that of atropine (Nagumo et al. 1998).

RESULT AND DISCUSSION
A number of elegant total syntheses have been reported for TAN1251 A, C and D (Snider & Lin, 2000; Nagumo et al. 1998, 2002; Wardrop & Basak, 2001; Ousmer et al. 2001; Auty et al. 2004; Mizutani et al. 2002, 2005). However, only Snider and Lin (2000) remain the only group to synthesis (+)-TAN1251B, which utilized a 1,3-dipolar cycloaddition of nitroene to construct the skeleton.

We have recently reported the synthesis of the tricyclic core of (−)-FR901483 (5) (Asari et al. 2007), the biosynthetically related compounds of TAN1251 series (Figure 2).

Consequently, both molecules share the same targeted precursor, 5,6-spirocyclic enone 7, which can be utilized by an alkylidene carbene insertion reaction and the oxidative cleavage/aldol dehydration sequence according to our previous synthetic route.

The cyclisation precursor, vinyl chloride 13 can be obtained in quantitative yield from the protected cis-hydroxy-D-proline 11 in 4 steps sequence, which includes the reduction, Wittig reaction and hydrogenation (Figure 3).

With the 5,6-spirocycles 7 of the natural product constructed, the task of incorporating the regioselective hydroxyl moiety of TAN1251B was undertaken.

Our retrosynthetic analysis in Figure 4 reveals that the presence of the double bond in our substrate 7 would give an advantage to control the regioselectivity of the α-hydroxylation reaction by blocking one of the α-keto sites.
HYDROXYLATION STUDIES

There are numerous methods for preparing α-hydroxy ketone described in the literature. However, only Moriarty’s protocol (1981, 1987) seems to offer the high levels of regioselectivity.

Treatment of 7 with iodosobenzene (PhI=O) in the presence of NaOH resulted in the formation of an impure inseparable mixture of diastereoisomers products 14 and 16 in 41% combined yield, together with other unidentified byproducts (Figure 5).

Since the OTBS group is believed to be the caused for the selectivity problem and the lower yield, we decided to change the OTBS group with an azide. Hence, the TBS group was deprotected with TBAF to give 17 in 76% yield (Scheme 5). The hydroxyl functionality in 17 was activated as its mesylate by reaction with methanesulphonyl chloride (MsCl) in the presence of base, which was then displaced with NaN₃ at an elevated temperature to deliver the azide 19 in 84% yields.
Hydroxylation of the enolate of 19 with PhI=O gave about 79% of a 1:1.2 mixture of 20 and 21 (Figure 7). The successful hydroxylation leading to 20 and 21 without oxidation of the double bonds or amines was encouraging.

The structure of 20 and 21 were tentatively assigned on the basis of the NOE between the CHOH peak at C(7) in 21 as being an equatorial, due to the presence of an nOe from H-7 to both H-4' and 4'' (2-5%) (Figure 8).


Iodosylbenzene (141 mg, 0.64 mmol) and NaOH (23.5 mg, 0.58 mmol) were added to a stirred solution of 19 (171 mg, 0.58 mmol) in dry MeOH (10 mL) under argon at 0 °C. The mixture was stirred for 3 hours. The reaction was quenched with 2 M HCl (30 mL) and then extracted with CHCl3 (4 × 30 mL). The combined organic extracts were dried (MgSO4) and the solvent was removed in vacuo. The crude product was purified by flash column chromatography using petrol and EtOAc (1:1), increasing polarity to EtOAc to afford the product 19 (179 mg, 84%) as a colourless oil: [α]D19 = 29.2 (c 1.39, CHCl3); δ (270 MHz, DMSO, 80 °C): 6.92 (1H, dd, J 10.2, 2.2, C=H), 5.80 (1H, dd, J 10.2, 0.9, C=H), 4.39 (1H, quin, J 6.0, C=H), 3.71 (1H, dd, J 11.3, 6.2, C=H), 3.43 (1H, ddd, J 11.4, 5.4, 0.8, C′=H), 2.78-2.49 (3H, m, CH3), 2.45-2.33 (1H, m, CH), 2.11-1.91 (2H, m, CH2), 1.41 (9H, s, Boc-C(CH3)3); δc (400 MHz, CDCl3): Data were collected for a mixture of rotamers: Data for the major rotamer: 197.3 (C=O), 156.5 (CH), 127.3 (CH), 80.6 (C), 61.6 (C), 57.7 (CH), 51.8 (CH2), 41.7 (CH3), 35.2 (CH2), 32.2 (CH2); m/z (ES, +ve) Found 315.1436 (M+Na, C14H20NNaO3 requires 315.1433); νmax/cm−1 (CHCl3): 3015, 2978, 2103, 1803, 1582, 1393, 1368.

GENERAL EXPERIMENTAL PROCEDURE

High-resolution mass spectra were acquired on VG micromass 70E and AIMS 902 instruments, using electrospray positive ionisation or (ES, +ve). Infrared spectra were recorded using a Perkin-Elmer 1600 FT spectrophotometer as dilute solutions in chloroform (CHCl3). Microanalytical data were obtained using an Exeter Analytical CE-440 elemental analyser. Melting points were measured on a Gallenkamp apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-370 polarimeter and concentrations given as g/100 mL.

1H, 13C, COSY, NOESY, HMBC and HMQC NMR spectra were recorded using either a Bruker AV400 or a Jeol EX270 MHz spectrometer at room temperature unless otherwise stated.

EXPERIMENTAL PROCEDURE

Sodium azide (120 mg, 1.82 mmol) was added to a stirred solution of 19 (252 mg, 0.73 mmol) in dry DMF (10 mL) under argon. The mixture was stirred at 80°C for 2 days and then extracted with EtOAc (3 × 20 mL) from deionised water (25 mL). The combined organic extracts were washed with water (2 × 20 mL), dried (MgSO4) and the solvent was removed in vacuo. The crude product was purified by flash column chromatography using petrol and EtOAc (1:1), increasing polarity to EtOAc to afford the product 19 (179 mg, 84%) as a colourless oil: [α]D19 = 28.2 (c 1.39, CHCl3); δ (270 MHz, DMSO, 80 °C): 6.92 (1H, dd, J 10.2, 2.2, C=H), 5.80 (1H, dd, J 10.2, 0.9, C=H), 4.39 (1H, quin, J 6.0, C=H), 3.71 (1H, dd, J 11.3, 6.2, C=H), 3.43 (1H, ddd, J 11.4, 5.4, 0.8, C′=H), 2.78-2.49 (3H, m, CH3), 2.45-2.33 (1H, m, CH), 2.11-1.91 (2H, m, CH2), 1.41 (9H, s, Boc-C(CH3)3); δc (400 MHz, CDCl3): Data were collected for a mixture of rotamers: Data for the major rotamer: 197.5 (C=O), 156.7 (CH), 153.1 (C=O), 126.7 (CH), 81.2 (C), 61.3 (C), 57.2 (CH), 51.7 (CH2), 42.8 (CH3), 35.5 (CH2), 33.7 (CH2), 28.3 (CH3). Data for the minor rotamer, where different from the major rotamer: 197.3 (C=O), 156.5 (CH), 127.3 (CH), 80.6 (C), 61.6 (C), 57.7 (CH), 51.8 (CH2), 41.7 (CH3), 35.2 (CH2), 32.2 (CH2); m/z (ES, +ve) Found 315.1436 (M+Na, C14H20NNaO3 requires 315.1433); νmax/cm−1 (CHCl3): 3015, 2978, 2103, 1803, 1582, 1393, 1368.
2.09 (1H, dd, J 13.2, 6.2, CH_2), 1.40 (9H, s, Boc-C(CH_3)_2); δ_C (400 MHz, DMSO, 80 °C): 199.5 (C=O), 156.5 (CH), 153.0 (C=O), 125.1 (CH), 80.2 (C), 70.5 (CH), 62.8 (C), 57.8 (CH), 51.8 (CH2), 42.7 (CH2), 42.7 (CH2), 28.6 (CH3); m/z (ES, +ve) Found 331.1376 (M+Na, C_{14}H_{20}N_{4}NaO_{4} requires 331.1377); ν_{max}/cm^{-1} (CHCl_3): 3426 (OH), 2981, 2104, 1686 (C=O), 1394, 1368.

SUMMARY
In summary, we have successfully utilised an alkylidene carbene insertion reaction to construct the quartenary centre, and performed the oxidative cleavage/aldol dehydration sequence to furnish the 5,6-spirocyclic enone, the precursor of TAN1251B. This work also highlights the successful of incorporating the hydroxyl moiety at the alpha position of the 5,6- spirocyclic enone.

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